Medical Policy Manual Transplant, Policy No. 45.22

Hematopoietic Cell Transplantation for Multiple Myeloma and POEMS Syndrome

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic cell transplantation may be considered **medically necessary** to treat multiple myeloma or POEMS syndrome with either of the following (A. or B.):

   A. Single initial or second (salvage) transplant to treat multiple myeloma.

   B. Single initial transplant to treat POEMS syndrome.

II. Tandem hematopoietic cell transplantation may be considered **medically necessary** to treat newly diagnosed (see Policy Guidelines) multiple myeloma after induction therapy with either of the following (A. or B.):

   A. Autologous-autologous tandem hematopoietic cell transplant.

   B. Tandem transplantation with an initial autologous hematopoietic cell transplant followed by reduced-intensity conditioning allogeneic hematopoietic cell transplant.

III. Hematopoietic cell transplantation is considered **investigational** in the treatment of multiple myeloma or POEMS syndrome with any of the following (A.-D.):

A. Third or higher autologous hematopoietic cell transplantation in the treatment of multiple myeloma.

B. Tandem hematopoietic cell transplantation for POEMS syndrome.

C. Myeloablative or nonmyeloablative (reduced intensity conditioning) allogeneic hematopoietic cell transplantation as initial transplant for multiple myeloma, or as salvage therapy (after a failed prior course of autologous hematopoietic cell transplantation).

D. Allogeneic hematopoietic cell transplantation to treat POEMS syndrome.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Induction therapy**: The initial chemotherapy given after diagnosis and prior to hematopoietic cell transplantation. Induction therapy is also referred to as primary and frontline therapy.
- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant, including specific type of transplant being requested (single initial or second [salvage] autologous transplant vs. tandem hematopoietic cell transplant)

CROSS REFERENCES

1. Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification, Genetic Testing, Policy No. 70

2. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
3. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the

patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the condition with lower doses or less-intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

MULTIPLE MYELOMA (MM)

Multiple myeloma is a systemic malignancy of plasma cells that represents a small but significant proportion of all hematologic cancers. It is treatable but rarely curable, with estimated new cases and deaths in 2023 in the U.S. of 35,730 and 12,590, respectively.[1] At the time of diagnosis most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease.

The disease is staged by estimating tumor mass, based on various clinical parameters like hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure.[1] Multiple myeloma usually evolves from an asymptomatic premalignant stage (termed “monoclonal gammopathy of undetermined significance” or MGUS). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic multiple myeloma prolongs survival when compared to therapy delivered at the time of symptoms or end-organ damage.[1, 2] In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized, and referred to as smoldering multiple myeloma.[3] The overall risk of disease progression from smoldering to symptomatic multiple myeloma is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 years.[2]

POEMS SYNDROME

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia.[4, 5] This complex, multiorgan disease was first described in 1938, but the acronym – POEMS -

was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.[6] No single test establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence suggests it is mediated by imbalance of proinflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved.[5, 7] However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in the table below. Both mandatory major criteria, at least one of the other major criteria, and at least one of the minor criteria are necessary for diagnosis.[8]

Criteria for the Diagnosis of POEMS Syndrome[8]

Mandatory Major Criteria	Other Major Criteria	Minor Criteria	Other Symptoms and Signs
• Polyneuropathy • Monoclonal plasma-proliferation disorder	• Sclerotic bone lesions • Castleman disease • Vascular endothelial growth factor elevation	• Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Edema (edema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails) • Papilledema • Thrombosis/ polycythemia	• Pulmonary hypertension/ restrictive lung disease • Thrombotic diatheses • Low vitamin B12 values • Diarrhea • Clubbing • Weight loss • Hyperhidrosis

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.[9] Other large series have been described in the United States, France, China, and India.[8] In general, patients with POEMS have a superior overall survival compared with that of multiple myeloma; with one study reporting a median survival of nearly 14 years, in a large series from the Mayo Clinic.[7] However, given the rarity of POEMS, there is a paucity of RCT evidence for POEMS therapies.[8] Numerous approaches have been tried, including ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylating agents, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) support.[5, 7] Optimal treatment involves eliminating the plasma cell clone, for example by surgical excision or local radiation therapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. The therapeutic approach to POEMS differs based on the presence of disseminated disease, commonly determined by the presence of bone marrow involvement and/or the presence of multiple skeletal lesions.[5] Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, also have been investigated.[5, 10]

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of multiple myeloma (MM) or POEMS syndrome, comparative clinical trials that compare this therapy to standard medical treatment, such as standard conditioning regimens, are needed. Further, for treatment of hematologic malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

NEWLY DIAGNOSED MULTIPLE MYELOMA

Risk-Adapted Therapy

The approach to the treatment of newly diagnosed MM (symptomatic) is dictated by eligibility for autologous hematopoietic cell transplantation (HCT) and risk stratification.[11] Risk stratification, using fluorescent in situ hybridization and conventional karyotyping divides patients into high- or standard-risk categories.

High-risk patients, which comprise approximately 25% of patients with MM, are defined by any of the following cytogenetic findings: a 17p deletion; translocations of chromosomes 4 and 14, chromosomes 14 and 16, chromosomes 14 and 20;a chromosome 13 deletion; or hypodiploidy or a 1q gain.[12] Standard-risk patients are those with hyperdiploidy (translocations of chromosomes 11 and 14 and chromosomes 6 and 14).

High-risk patients are generally treated with a bortezomib-based induction followed by autologous HCT and then bortezomib-based maintenance.[12] Standard-risk patients are typically treated with bortezomib-based induction therapy followed by autologous HCT and then maintenance with lenalidomide; however, if the patient is tolerating the induction regimen well, an alternative strategy would be to continue the initial therapy after hematopoietic cell collection, reserving the transplant for the first relapse.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION VERSUS STANDARD CHEMOTHERAPY

Systematic Reviews

Lin (2023) conducted systematic review (SR) and meta-analysis to improve understanding of the benefit of HCT directly after induction therapy.[13] Seven RCTs and 15 observational studies that compared upfront ASCT to no upfront ASCT were included. Overall risk of bias in the RCTs was low, but the authors note that drop-out rates after randomization were higher in the no ASCT group. Six of the observational studies had high risk for bias. Complete response (CR) ($p= 0.03$), PFS ($p < 0.00001$), and OS ($p < 0.00001$) were higher with upfront ASCT. Older age ($p=0.002$), female gender ($p=0.023$), and shorter follow-up duration ($p=0.013$) were associated with longer OS, while high-risk genetics was associated with longer PFS ($p=0.04$) and OS ($p=0.021$).

Gao (2021) published a systematic review (SR) after performing a PubMed, Embase and Cochrane Library database until July 31, 2021.[14] This SR took into consideration, all eligible studies comparing progression-free survival (PFS), overall survival (OS), optimal treatment response after autologous HCT in MM. In this study they compared a high-dose melphalan (HDMEL, 200 mg/m2) response versus melphalan with busulfan (BUMEL) in newly diagnosed MM patients having undergone autologous HCT. This SR identifies BUMEL-based conditioning as a likely alternative strategy to improve autologous HCT outcomes in MM.

An SR with meta-analysis by Mian (2020) specifically sought to examine the impact of autologous HCT in patients aged 65 years or older with newly-diagnosed MM.[15] This review included data from two RCTs and six observational studies. In a pooled analysis of the observational studies, autologous HCT was associated with favorable effects on OS compared to non-HCT therapy (hazard ratio, 0.44; 95% CI, 0.34 to 0.58; p<0.0001). However, in the pooled analysis of RCT data, the impact of autologous HCT on OS was uncertain (hazard ratio, 0.94; 95% CI, 0.25 to 3.54, p=0.93). Observational data also showed higher CR rates with autologous HCT (odds ratio, 5.06; 95% CI, 2.60 to 9.88; p<0.0001). The authors of the review concluded that autologous HCT may improve the OS and CR rates in elderly patients based on observational data, but the quality of the evidence is very low and more studies are needed.

A meta-analysis of 2,411 patients enrolled in randomized controlled trials compared standard dose chemotherapy versus myeloablative chemotherapy with single autologous hematopoietic stem cell transplant (HCT).[16] The authors of the meta-analysis concluded that myeloablative therapy with autologous HCT increased the likelihood of PFS (hazard of progression=0.75; 95% CI: 0.59–0.96) but not OS (hazard of death=0.92; 95% CI: 0.74–1.13); the odds ratio for treatment-related mortality was 3.01 (95% CI: 1.64–5.50) in the group with autologous HCT. However, the effects of myeloablative chemotherapy and autologous HCT may have been diluted by the fact that up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HCT as salvage therapy when the MM progressed. This could account for the lack of a significant difference in OS between the two groups in the study.

Randomized Controlled Trials

Yong (2023) published results from a phase 2 randomized non-inferiority trial in which newly diagnosed patients with multiple myeloma were randomized to autologous HCT followed by carfilzomib maintenance, or to consolidation therapy (CT) using carfilzomib-cyclophosphamide-dexamethasone followed by carfilzomib maintenance.[17] The CARDAMON study randomized 218 patients and each group included 109 subjects. Of the 218 patients, 59/109 in CT group and 55/109 in the HCST group completed maintenance therapy. Two year progression-free survival was 75% (95% CI 65 to 82) in the HSCT group and 68% (95% CI 58 to 76) in the CT group, which indicates CT did not meet the criteria for non-inferiority (10% margin).

Richardson (2022) conducted a US-based, multicenter, open-label RCT comparing lenalidomide, bortezomib, and dexamethasone alone with the lenalidomide, bortezomib, and dexamethasone regimen in addition to autologous HCT plus melphalan in patients with newly diagnosed multiple myeloma.[18] All patients received daily maintenance lenalidomide until disease progression, unacceptable toxicity, or withdrawal from treatment or the trial. Patients treated with chemotherapy alone (n=357) had lower median PFS (46.2 months) compared with

those who received chemotherapy and autologous HCT (n=365; 67.5 months). Patients who received chemotherapy only had higher rates of disease progression or death at a median follow-up of 76 months (HR, 1.53; 95% CI, 1.23 to 1.91; p<.001). Overall survival was similar between groups. Grade 3 or higher treatment-related adverse events were higher in patients undergoing HCT (94.2% vs. 78.2%).

Cavo (2020) published the results of a multicenter (172 sites), open-label, phase 3 RCT comparing autologous HCT (n=702) with bortezomib-melphalan-prednisone (VMP) as intensification therapy (n=495) and bortezomib-lenalidomide-dexamethasone (VRD) consolidation therapy (n=449) with no consolidation (n=428) in previously untreated stage 1-3 MM patients.[19] Eligibility was based on the International Staging System (ISS), measurable disease (serum M protein >10 g/L or urine M protein >200 mg in 24 h or abnormal free light chain [FLC] ratio with involved FLC >100 mg/L, or proven plasmacytoma by biopsy), and WHO performance status grade 0-2 (grade 3 was allowed if secondary to myeloma). Patients were first randomly assigned (1:1) to receive either four 42-day cycles of bortezomib combined with melphalan and prednisone or autologous HCT after high-dose melphalan, stratified by site and ISS disease stage. In centers with a double HCT policy, the first randomization (1:1:1) was to VMP or single or double HCT. Afterwards, a second randomization assigned patients to receive two 28-day cycles of consolidation therapy with bortezomib, lenalidomide, and dexamethasone or no consolidation; both groups received lenalidomide maintenance therapy. Primary outcomes were PFS from the first and second randomizations, analyzed in the intention-to-treat population, which included all patients who underwent each randomization. Safety analyses included data from all patients who received at least one dose of study drugs. At a median follow-up of 60.3 months (IQR 52.2-67.6), median PFS was significantly improved with autologous HCT compared with VMP (56.7 months [95% CI 49.3-64.5] vs. 41.9 months [37.5-46.9]; hazard ratio [HR] 0.73, 0.62-0.85; p=0.0001). Two hundred thirty-nine (34%) of 702 patients in the autologous HCT group and 135 (27%) of 495 in the VMP group had at least one serious adverse event. The most common grade ≥3 adverse events in the autologous HCT group compared to the VMP group included neutropenia (513 [79%] of 652 patients vs. 137 [29%] of 472 patients), thrombocytopenia (541 [83%] vs. 74 [16%]), gastrointestinal disorders (80 [12%] vs. 25 [5%]), and infections (192 [30%] vs. 18 [4%]). Thirty-eight (12%) of 311 deaths from first randomization were likely to be treatment related: 26 (68%) in the autologous HCT group and 12 (32%) in the VMP group, most frequently due to infections (eight [21%]), cardiac events (six [16%]), and second primary malignancies (20 [53%]). This study was funded by Janssen and Celgene.

In a randomized, open label phase 3 trial from the Intergroupe Francophone Myelome (IFM)/Dana-Farber Cancer Institute (DFCI), Attal (2017) compared consolidation therapy using five cycles of combination chemotherapy to HCT followed by two cycles of combination chemotherapy.[20] Seven hundred patients with symptomatic, measurable, newly diagnosed MM were randomized to one of two treatment arms. All patients received induction therapy with three cycles of lenalidomide, bortezomib, and dexamethasone (RVD). As consolidation therapy, the transplant arm received high-dose melphalan and stem-cell transplantation followed by two cycles of RVD, whereas the chemotherapy arm received five additional cycles of RVD.

The primary end point was progression-free survival. Response rate, time to disease progression, overall survival, and adverse event rates were reported as secondary end points. A statistically significant difference between groups was reported for median progression-free survival, which was longer in the transplantation group than the chemotherapy-only group (50

and 36 months, respectively; adjusted hazard ratio for disease progression or death, 0.65; p<0.001). The benefit was found to apply to all patient subgroups tested. The difference in complete response rates was statistically significant, with a rate of 48% in the chemotherapy-alone group and 59% in the transplantation group (p=0.03). OS was not significantly different at four years between the transplantation group and the chemotherapy-only group (81 and 82%, respectively). The transplantation group had significantly higher rate of grade 3 or 4 neutropenia (92%), rate of grade 3 or 4 gastrointestinal disorders (28%), and rate of infections (20%) than the chemotherapy only group (47, 7, and 9%, respectively).

Gay (2015) compared autologous HCT to standard chemotherapy plus lenalidomide, a newer agent for treatment of MM.[21] The study was an open label RCT from 59 centers in Europe and Australia that used a 2x2 factorial design to compare four groups 1) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide alone, 2) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide and prednisone 3) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide alone, and 4) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide plus prednisone. The primary outcome for this study was progression-free survival. (PFS), and mean followup at the time of publication was 52 months. Median PFS was superior for the HCT group compared to chemotherapy plus lenalidomide (43.3 months, 95% CI 33.2-52.2months vs 28.6 months, 95% CI 20.6-36.7mths, p<0.0001). The rate of grade 3 or 4 adverse events was higher for the HCT group compared to chemotherapy for hematological events (84% vs 26%), gastrointestinal complications (20% vs 5%), and infections (19% vs 5%).

Data are available from seven randomized trials of autologous HCT following induction therapy that were designed and implemented prior to the availability of thalidomide, lenalidomide, and bortezomib.[22-28] The introduction of these agents has dramatically changed the treatment paradigm of multiple myeloma. Trials incorporating these newer agents into induction regimens are ongoing. Preliminary results have shown CRs in a substantial proportion of these patients, opening the question as to what role autologous HCT will continue to play a role. However, it will require further follow-up to determine if these newer induction regimens will translate into improved survival.[29]

In all but one (Barlogie, 2006) of the seven studies, the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HCT arm.[27] This study published final results of the S9321 trial, which was initiated in 1993, and randomized 516 patients with MM to receive either standard therapy or myeloablative conditioning with melphalan 140 mg/m^2 plus total body irradiation followed by autologous HCT.[27] The authors reported virtually no difference in outcomes, including response rates, progression-free survival, and OS. In five of the seven studies, the superior CR rate translated into a significant increase in PFS. However, in the two studies that did not show an improved PFS with autologous HCT, randomization was not performed at diagnosis, but only after induction treatment, possibly introducing selection bias.[28] Three of the seven studies showed superior OS in the autologous HCT group.[22, 23, 25] The Intergroupe Francophone du Myélome (IFM) showed the superiority of high-dose chemotherapy and autologous HCT compared to conventional chemotherapy in a randomized trial of 200 patients younger than 65 years of age.[22] The group that underwent autologous HCT had significantly improved response rates, event-free and overall survival. Seven years later, the British Medical Research Council published similar results.[23]

The reasons for the discrepant results among these randomized studies are uncertain, but may be related to the conditioning regimens or patient age.

Nonrandomized Studies

Villalba (2022) analyzed data from 35 hospitals in the Spanish Myeloma Group.[30] Patients (N=213) with newly diagnosed multiple myeloma and high-risk cytogenetics underwent single (n=142) or tandem (n=71) autologous HCT. At a median follow-up of 31 months, PFS was not significantly longer with tandem HCT compared with single HCT (48 vs. 41 months; p=.33). Patients receiving tandem HCT were younger, had more advanced stage disease, and a higher plasma cell infiltration at diagnosis. More patients in the single-transplant group died by the time of analysis than those undergoing tandem transplant although this was not statistically significant (23% vs. 12.7%; p=.09). The authors concluded that tandem HCT partly overcomes the poor prognosis of high-risk cytogenetics when compared with a single HCT but noted further study is needed.

Lemieux (2021) published the results of a retrospective analysis of autologous HCT (AHCT, n=38) compared to non-transplant therapy (n=41) in patients with multiple myeloma age 70 years and older treated at a single center.[31] AHCT was not pursued because of patient or physician preference in 80% (n = 33) or ineligibility in 20% (n = 8). Median PFS from treatment start in patients undergoing ASCT (n = 38) vs. not (n = 41) was 41 months vs. 33 months, p = 0.03. Further, AHCT was an independent favorable prognostic factor for PFS in multivariate analysis, after accounting for HCT-CI score, performance status, hematologic response, and maintenance. No difference in OS was found, with estimated five-year OS of 73% vs. 83%, respectively (p = 0.86). In addition, similar PFS was found in this cohort as in an institutional cohort of patients age less than 70 years (n = 631, median PFS from transplant: 36 vs. 47 months, p = 0.25).

Marini (2019) published a retrospective study of elderly (age 65 years or older) MM patients treated with autologous HCT (n=132) compared to non-transplanted patients with similar clinical characteristics (n=23) at a single center between 2010 and 2016.[32] The median follow-up for transplant patients and controls was 30 months. The overall transplant-related mortality rate was 3.8%, and the transplant group had a higher survival rate than the control group (OS 59 and 30 months, respectively, p=0.037; event-free survival 45 and 27 months, respectively, p=0.014). The study was limited by its retrospective nature, lack of randomization, and the subjective categorization for transplant of patients.

Section Summary: Autologous Hematopoietic Cell Transplantation Versus Standard Chemotherapy

For individuals with newly diagnosed MM, evidence from multiple RCTs has suggested that high-dose chemotherapy with autologous HCT is superior to standard chemotherapy in PFS, and possibly OS. More recent RCTs comparing high-dose melphalan plus autologous HCT to chemotherapy regimens that include novel agents have also shown that high-dose melphalan plus autologous HCT improves PFS.

RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Despite improved survival rates with autologous HCT versus conventional chemotherapy, many patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HCT include regimens utilizing newer agents (eg, daratumumab- and bortezomib-based regimens), regimens utilizing traditional chemotherapy, or a second HCT.[12]

SALVAGE TRANSPLANTATION

Despite the success in improved survival with autologous HCT versus conventional chemotherapy, nearly all patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HCT include novel biologic agents (e.g., thalidomide, lenalidomide and bortezomib, as single agents, in combination with dexamethasone, and in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HCT. No clear standard of care exists.

Repeat Autologous HCT for Relapse after Initial Autologous HCT

Systematic Reviews

An evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from four relevant clinical series.[33] Investigators reported that some myeloma patients who relapsed after a first autotransplant achieved durable complete or partial remissions after a second autotransplant as salvage therapy. Factors that apparently increased the likelihood of durable remissions and extended survival included a chemosensitive relapse, younger age, a long disease-free or progression-free interval since the initial autotransplant, and fewer chemotherapy regimens prior to the initial autotransplant. Thus, clinical judgment plays an important role in selecting patients for this treatment with a reasonable likelihood that potential benefits may exceed harms.

Randomized Controlled Trials

Goldschmidt (2020) conducted a randomized, open-label, multicenter phase 3 study (the ReLApsE trial) in patients aged 18 to 75 years with a first to third relapse of MM.[34] These patients had previously undergone autologous HCT and attained remission of at least 12 months prior to relapse. Patients were randomized to receive a repeat autologous HCT (n=139) or continuous therapy with lenalidomide plus dexamethasone (n=138). Patients who underwent repeat autologous HCT also received reinduction therapy with lenalidomide plus dexamethasone, salvage high-dose chemotherapy with melphalan, and lenalidomide maintenance. In the primary ITT analysis, no significant differences were seen in PFS (median, 20.7 months vs. 18.8 months for transplant vs. control; hazard ratio, 0.87; 95% CI, 0.65 to 1.16; p=0.34) or OS (median not reached in the transplant group vs. 62.7 months in the control arm; hazard ratio, 0.81; 95% CI, 0.52 to 1.28; p= 0.37). However, only 71% of patients assigned to the transplant group actually underwent salvage high-dose chemotherapy and autologous HCT. Post hoc analyses found that the patients who received salvage high-dose chemotherapy and autologous HCT had a trend toward superior PFS compared to the control group, and statistically superior OS (median not reached vs. 57 months; hazard ratio, 0.56; 95% CI, 0.32 to 0.99; p=0.046).

In 2014, Cook published a multicenter, randomized, open-label, phase 3 study from 51 centers across the United Kingdom, that included patients aged at least 18 years with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT.[35] Before randomization, eligible patients received bortezomib, doxorubicin, and dexamethasone (PAD) induction therapy and then underwent peripheral blood stem cell mobilization and harvesting, if applicable. Eligible patients were randomly assigned (1:1) to receive either high-dose melphalan 200 mg/m2 plus salvage autologous HCT or oral cyclophosphamide (400 mg/m2/wk for 12 weeks). The primary end point was time to disease progression, analyzed by intention to treat. A total of 297 patients were enrolled, of whom 293

received PAD reinduction therapy. Among the latter, 174 patients with sufficient harvest of peripheral blood stem cells were randomly allocated to undergo salvage HCT (n=89) or receive cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HCT group than in the cyclophosphamide group (19 months [95% CI, 16 to 25] vs 11 months [95% CI, 9 to 12]; hazard ratio=0.36 [95% CI, 0.25 to 0.53]; p<0.001). Frequently reported (>10% of patients) grade 3-4 morbidity with PAD induction, salvage HCT, and cyclophosphamide were: neutropenia (125 [43%] of 293 patients after PAD and 63 [76%] of 83 patients in the salvage HCT group vs 11 [13%] of 84 patients in the cyclophosphamide group), thrombocytopenia (150 [51%] after PAD, and 60 [72%] vs four [5%], respectively), and peripheral neuropathy (35 [12%] after PAD, and none vs none, respectively). This study provides additional evidence for a net benefit of high-dose melphalan plus salvage HCT when compared with cyclophosphamide in patients with relapsed MM eligible for intensive therapy.

Final survival data for the trial was reported in 2016.[36] The HCT group had superior overall median survival compared to the chemotherapy group (67 months, 95% CI 55mths-not estimable vs 52 months, 95% CI 42-60mths, p<0.0001). Time to disease progression continued to favor the HCT group at the longer followup (19 months, 95% CI 16-26mths vs. 11 months, 95% CI 9-12mths, p=0.02). There were no further adverse events related to the HCT procedure reported during longer followup. The cumulative incidence of second malignancies was 5.2% (95% CI 2.1-8.2%).

Nonrandomized Studies

Olin (2008) reported their experience with 41 patients with multiple myeloma who received a second salvage autologous HCT for relapsed disease.[37] Median time between transplants was 37 months (range 3–91 months). Overall response rate in assessable patients was 55%. Treatment-related mortality was 7%. Median follow-up time was 15 months, with median PFS of 8.5 months and median OS 20.7 months. In a multivariate analysis of OS, the number of prior lines of therapy (≥5) and time to progression after initial transplant were the strongest predictors of OS.

Although not conclusive, available evidence on the use of autologous transplant following relapse is sufficient to suggest treatment benefit.

Allogeneic HCT for Relapse after Initial Autologous HCT

Nonrandomized Studies

Ikeda (2019) published a retrospective analysis of registry data evaluating OS in patients who underwent follow-up HCT for relapsing/progressing MM after prior autologous HCT.[38] The analysis included patients receiving allogeneic HCT (allogeneic HCT, n=192) and autologous HCT (ReASCT; n=334). The OS analysis was stratified by risk based on variables including sex, previous response to SCT, and duration from prior autologous HCT. OS was higher in ReASCT than allogeneic HCT in the intermediate-risk subgroup, which comprised the largest population (28.2% vs. 21.5%, p<0.004). No significant advantage of allogeneic HCT over ReASCT in the low- or high-risk subgroups was observed. The authors reported that long-term survival patients were noted only in the allogeneic HCT group, which supports the need of additional research into allogeneic HCT for specific patient groups.

Schneidawind (2017) reported on consecutive patients (N=41) who received an allogeneic HCT for the treatment of relapsed or refractory MM from 2001 to 2015. Ninety five percent of patients had previously received autologous HCT (18 tandem; 21 single high-dose chemotherapy followed by autologous HCT). Allogeneic HCT following the single approach was associated with an increased 3-year EFS (24% vs 6%, P=0.04) and OS (64% vs 35%, p=0.09) compared with a tandem autologous approach. Additionally, allogeneic HCT following the tandem autologous approach was associated with an increased relapse/progression rate (72% vs 58%, p=0.30).

Qazilbash reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant.[39] Fourteen patients (median age: 52 years) received a second autologous transplant and 26 patients (median age: 51 years) underwent a reduced-intensity allogeneic transplant. Median interval between first and second transplant was 25 and 17 months for the autologous and allogeneic groups, respectively. After a median follow-up of 18 months (range: 2 to 69 months) for the autologous group, median PFS was 6.8 months and OS 29 months. After a median follow-up of 30 months (range: 13 to 66 months) for the allogeneic group, median PFS was 7.3 months and OS 13 months. On univariate analysis, in the allogeneic group, an interval of greater than 1 year between the first and salvage transplants predicted a significantly better OS (p=0.02). None of the prognostic factors that were evaluated for the allogeneic group was found to have a significant impact on survival in the autologous group (which included age, cytogenetics, type of donor, and chronic graft-versus-host disease [GVHD], among others).

The European Group for Blood and Marrow Transplant (EBMT) reported an analysis of 413 patients who received a related or unrelated RIC allogeneic HCT for the treatment of relapse or disease progression after a prior autologous HCT.[40] Median age at RIC allogeneic HCT was 54 years, and 45% of patients had undergone two or more prior autologous transplants. The median OS and PFS from the time of allogeneic transplantation for the entire population were about 25 and 10 months, respectively. Cumulative non-relapse mortality (NRM) at one year was about 22%. In a multivariate analysis, cytomegalovirus (CMV) seronegativity of both patient and donor was associated with significantly better PFS, OS and NRM. Patient-donor gender mismatch was associated with better PFS. Fewer than two prior autologous transplants was associated with better OS and shorter time from the first autologous HCT to the RIC allogeneic HCT was associated with lower NRM. Findings suggested patient and donor CMV seronegativity may represent key prognostic factors for outcome after RIC allogeneic HCT in cases of relapse or progression following one or more autologous transplants.

Evidence on the use of allogeneic transplant as salvage treatment after initial autotransplant is not suggestive of increased treatment benefit compared with autologous transplant.

TANDEM TRANSPLANT

A tandem transplant involves an autologous transplant followed by a preplanned second transplant, either another autologous or a reduced-intensity conditioning (RIC) allogeneic transplant. A tandem transplant differs from a second, salvage transplant in that a tandem transplant involves prospective planning for a second transplant at the time the first transplant is being planned.

Tandem Autologous-Autologous HCT

Randomized Controlled Trials

In the RCT by Cavo (2020) described above, patients who were assigned to receive autologous HCT at a center that performed double autologous HCT were randomly assigned to receive either single (n=209) or double (n=210) autologous HCT.[19] Outcomes were compared between these subgroups in a secondary analysis. Double autologous HCT significantly improved rates of 5-year PFS (53.5% vs. 44.9%; hazard ratio, 0.74; 95% CI, 0.56 to 0.98; p=0.036) and 5-year OS (80.3% vs. 72.6%; hazard ratio, 0.62; 95% CI, 0.41 to 0.93; p=0.022) compared to single autologous HCT. Patients with high-risk cytogenetic profiles appeared to attain a greater magnitude of benefit with double HCT versus single HCT, compared to patients with standard-risk profiles.

Stadtmauer (2019) reported a randomized phase 3 study in patients with symptomatic MM who received at least two cycles of any regimen as initial systemic therapy without disease progression and who were within 2 to 12 months of the first dose of initial therapy.[41] Patients were randomly assigned to one of three treatment arms: autologous HCT (n=257), tandem autologous HCT (n=247), or autologous HCT plus four cycles of lenalidomide, bortezomib, and dexamethasone (n=254). Rates of 38-month PFS were similar across groups (58.5%, 57.8%, and 53.9% for tandem HCT, autologous HCT plus lenalidomide/bortezomib/dexamethasone, and autologous HCT respectively), as were rates of 38-month OS (81.8%, 85.4%, and 83.7%, respectively). However, 32% of patients in the tandem group did not receive the second HCT. Results of this study differed from those of the Cavo study described above. This may be related to differences in initial therapy; in the Cavo study, patients received a prespecified number of induction therapy cycles that did not include immunomodulatory agents (eg, lenalidomide), while the majority of patients in this study received immunomodulatory agents as part of their initial therapy prior to transplant. Additionally, more patients in the Cavo study underwent tandem HCT as assigned (only 20% did not receive the second transplant).

The results of a 5-year follow-up of the trial by Stadtmauer et al (2019) were posted to Clinicaltrials.gov (NCT02322320) but have not been identified in a peer-reviewed journal.[42] Per Clinicaltrials.gov, the proportion of patients achieving PFS was similar for autologous HCT (45%), tandem autologous HCT (47.7%), and autologous HCT plus lenalidomide, bortezomib, and dexamethasone (44.1%); pairwise comparisons between treatment arms did not reach statistical significance. Likewise, the proportion of patients achieving OS was similar for autologous HCT (76.4%), tandem autologous HCT (74.7%), and autologous HCT plus lenalidomide, bortezomib, and dexamethasone (75.4%); pairwise comparisons between treatment arms did not reach statistical significance.

The Bologna 96 clinical study (2007), compared single with double autologous HCT (n=321).[43] Patients undergoing tandem autologous HCT were more likely than those with a single autologous HCT to attain at least a near complete response (47% vs. 33%; p=0.008), to prolong relapse-free survival (median, 42 vs. 24 months; p<0.001), and extend event-free survival (median, 35 vs. 23 months; p=0.001). There was no significant difference between the groups in treatment-related mortality (3 to 4%). There was a trend for improved OS among patients in the double-transplantation group (7-year rate of 60%) as compared with the single-transplantation group (7-year rate of 47%; p=0.10). Conversely, among patients achieving CR or near CR after one transplant, EFS and OS were not significantly different according to transplantation(s) received by study randomization. A subgroup analysis of outcomes of patients assigned to the two treatment arms was evaluated according to response, and showed similar results to the Attal study (described below), in that the benefit of a second transplant was seen only in patients that did not achieve at least a very good partial response with the first transplant.[44] However, the methodological shortcomings limit reliability of this

finding.

The first randomized trial of autologous tandem transplants (IFM-94) was published in December 2003 by Attal and randomized patients with newly diagnosed (i.e., previously untreated) myeloma to single or tandem autologous transplants.[44] Outcomes were analyzed by intention-to-treat at 75 months' median follow-up. Among those randomized to single transplants (n=199), 148 relapsed: 33 were salvaged with a second autotransplant, 13 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Among those randomized to tandem autotransplants (n=200), 129 patients experienced disease relapse: 34 received salvage therapy with another (3rd) transplant, 12 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Seven years after diagnosis, patients randomized to tandem transplants had higher probabilities than those randomized to single transplants for event-free (EFS; 20% vs. 10%, p=0.03), relapse-free (RFS; 23% vs. 13%; p<0.01), and overall (OS; 42% vs. 21%, p=0.010) survival. Treatment-related mortality was 6% and 4% after tandem and single transplants, respectively (p=0.40). Second transplants apparently extended survival only for those who failed to achieve a complete (CR) or very good partial response (VGPR) after one transplant (OS at seven years: 43% vs. 11%, p<0.001), however the methodological shortcomings limit reliability of this finding (comparing outcomes in subgroups was not one of the study objectives, study was not adequately powered for subgroup analyses).

An accompanying editorial by Stadtmauer raised concerns that these results might be specific to the regimens used for myeloablative therapy in IFM-94.[45] Patients in the single transplant arm received 140 mg/m^2 melphalan plus total-body irradiation (TBI), while those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. The editorial cites an IFM-95 study as evidence, suggesting 140 mg/m^2 melphalan plus TBI may be less effective and more toxic than myeloablative therapy than 200 mg/m^2 melphalan and no TBI. Based on this, the author hypothesizes increased survival in the IFM-94 tandem arm may have resulted from greater cumulative exposure to melphalan (280 vs. 140 mg/m2).

Results from available RCTs demonstrated small but significant clinical improvements with tandem autologous transplants among treatment naïve patients; such evidence may be suggestive of a treatment benefit. However, methodological limitations demonstrate the need for additional clinical trials.

Subsection Summary: Tandem Autologous Hematopoietic Cell Transplantation

Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improves OS and recurrence-free survival in newly diagnosed MM. Two recent RCTs found conflicting results on the benefit of tandem autologous HCT versus single autologous HCT; however, the study that found no additional benefit with tandem autologous HCT had a higher rate of nonadherence to the second planned HCT. Differences in initial therapy regimens between trials may also have led to conflicting results.

Tandem Autologous HCT Followed by Reduced-Intensity Conditioning (RIC) and Allogeneic HCT

Several randomized controlled trials have been published comparing RIC-allogeneic HCT following a first autologous HCT to autologous transplants, single or in tandem. These studies were based on "genetic randomization," that is, patients with an HLA-identical sibling were

offered an RIC-allogeneic HCT following the autologous HCT, whereas the other patients underwent either one or two autologous transplants.

Maffini (2018) published long-term follow-up results for MM patients treated with tandem autologous-allogeneic HCT.[46] The study consisted of 209 patients (86%) who received tandem HCT upfront and 35 patients (14%) who received tandem HCT after failing a previous autologous HCT. Median follow-up was 8.3 years. Five-year OS and PFS were 54% (95% CI: 48 to 60%) and 31% (95% CI: 25 to 36%), respectively; 10-year OS and PFS were 41% (95% CI: 34 to 48%) and 19% (95% CI: 13 to 24%), respectively. Overall non-relapse mortality was 2% at 100 days and 14% at 5 years.

Krishnan conducted a Phase 3 trial, published in 2011, comparing tandem autologous-autologous HCT (auto-auto group) versus tandem autologous-RIC allogeneic HCT (auto-allo group) in patients from 37 transplant centers in the U.S., who between 2003 and 2007, had received an autologous HCT (n=710).[47] Of these patients, 625 had standard-risk disease and 156 of 189 patients (83%) in the auto-allo group and 366 of 436 (84%) in the auto-auto group received a second transplant. Patients were eligible if they were younger than 70 years of age and had completed at least three cycles of systemic therapy for myeloma within the past 10 months. Patients were assigned to receive a second autologous or allogeneic HCT based on the availability of an HLA-matched sibling donor. Patients in the auto-auto group subsequently underwent random assignment to observation (n=219) or maintenance therapy with thalidomide plus dexamethasone (n=217). Kaplan-Meier estimates of three-year PFS were 43% (95% CI: 36-51) in the auto-allo group and 46% (42 to 51) in the auto-auto group (p=0.67). OS also did not differ at three years (77% [95%CI 72 to 84] versus 80% [77 to 84]; p=0.19). Grade 3 to 5 adverse events between the two groups were 46% and 42%, respectively. The authors concluded that non-myeloablative allogeneic HCT after autologous HCT is not more effective than tandem autologous HCT for patients with standard-risk myeloma.

Rosinol (2008) reported the results of a prospective study of 110 patients with MM who failed to achieve at least near-complete remission after a first autologous HCT and were scheduled to receive a second autologous transplant (n=85) or an RIC-allogeneic transplant (n=25), depending on the availability of an HLA-identical sibling donor.[48] The autologous/RIC-allogeneic group had a higher CR rate (40% vs. 11%; p=0.001) and a trend toward a longer PFS (median 31 months vs. not reached, p=0.08). There was no statistical difference in EFS or OS between the two groups. The autologous/RIC-allogeneic group experienced a higher transplantation-related mortality rate (16% vs. 5%; p=0.07) and a 66% chance of chronic graft-versus-host disease.

One study by Bruno (2007) included 80 patients with an HLA-identical sibling and who were allowed to choose allografts or autografts for the second transplant (58 completed an autograft/allograft sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence).[49] The results among those completing tandem transplantation showed a higher complete response rate at the completion of the second transplant for the autograft/allograft group (55%) than for the autograft/autograft group (26%; p=0.004). EFS and OS were superior for the patients who underwent autologous-allogeneic transplantation (35 months vs. 29; p=0.02 and 80 months vs. 54; p=0.01, respectively). Analyzing the group with HLA-identical siblings versus those without, in a pseudo intention-to-treat analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The treatment-related mortality rate at two years was 2% in the double

autograft group and 10% in the autograft/allograft group; 32% of the latter group had extensive, chronic graft-versus-host disease.

The first published study by Garban (2006) included high-risk patients (including deletion of chromosome 13).[50] Sixty-five patients were in the autologous/RIC-allogeneic group and 219 in the autologous/autologous group. Based on the intention-to-treat analysis, there was better median EFS and OS in the autologous/autologous group (35 months versus 31.7; p=NS and 47.2 months versus 35; p=0.07, respectively). If results for only those patients who actually received the autologous/RIC-allogeneic (n=46) or tandem autologous transplants (n=166) were analyzed, the superior OS was again seen in the tandem autologous group (median 47.2 vs. 35 months; p=0.07). Updated results of this population were reported with a reference date of July 2008 by Moreau[51] Comparing the results of the 166 patients who completed the whole tandem autologous HCT protocol to the 46 patients who underwent the entire autologous/RIC-allogeneic program, no difference was seen regarding EFS (median 25 vs. 21 months, p=0.88), with a trend toward superior OS in favor of double autologous HCT (median OS 57 vs. 41 months; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

Although the results differ among the Garban/Moreau study[50, 51] and the other studies[47-49] the authors of the Moreau study suggested that this is due to different study designs. The Moreau study update focused on patients with high-risk disease and involved a conditioning regimen before the RIC-allogeneic transplant that may have eliminated some of the graft-versus-myeloma effect. Other contributing factors may have been non-uniform preparative regimens, different patient characteristics and criteria for advancing to a second transplant (i.e., only patients who failed to achieve a CR or near CR after the first autologous transplant underwent a second), and a small population in the allogeneic group in the Moreau study. The authors suggest that the subgroup of high-risk patients with de novo MM may get equivalent or superior results with a tandem autologous/autologous transplant versus a tandem autologous/RIC-allogeneic transplant, and that in patients with standard-risk and/or chemosensitive multiple myeloma, RIC allograft may be an option.

Interim Study Findings

An interim analysis of a European Group for Blood and Marrow Transplant (EBMT) study was presented as a conference abstract.[52] Previously untreated patients received vincristine, doxorubicin, dexamethasone (VAD) or VAD-like induction treatment, and had a response status of at least stable disease (i.e., complete or partial remission or stable disease) at the time of autologous transplantation, which was also the time point for study inclusion. Patients with an HLA-identical sibling proceeded to RIC-allogeneic transplantation, while those without a matched sibling received no further treatment or a second autologous stem-cell transplant (if treated within a tandem program). A total of 356 patients were included, with a median follow-up of 3.5 years. Of these, 108 patients were allocated to the RIC-allogeneic transplant group and 248 to the autologous transplant group. Of the patients allocated to the allogeneic group, 98 received a RIC-allogeneic transplant. At interim reporting, no significant differences in PFS or OS estimates were noted between groups.

Additional results from the EBMT trial were published by Gahrton (2013).[53] At 96 months in the EBMT trial, PFS and OS were 22% and 49% versus 12% (p=0.027) and 36% (p=0.030) with autologous/RIC-allogeneic (auto/RICallo) and autologous HCT, respectively. The corresponding relapse/progression rate (RL) was 60% versus 82% (p = 0.0002) and the non-

relapse mortality at 36 months was 13% versus 3% (p=0.0004) with auto/RICallo and autologous HCT respectively. In patients with the del(13) abnormality corresponding PFS and OS were 21% and 47% in the auto/RICallo group versus 5% (p=0.026), and 31% (p=0.154) in the autologous only group. Long-term outcome in patients with MM was better with auto/RICallo HCT as compared with autologous only and the auto/RICallo approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation. Authors called for longer follow-up periods of at least five years in order to better characterize the role of auto/RICallo HCT in patients with multiple myeloma.

Subsection summary: Tandem Autologous HCT Followed by Reduced-Intensity Conditioning (RIC) and Allogeneic HCT

Although the body of evidence has shown inconsistencies regarding OS and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allo-HCT, although at the cost of higher treatment-related mortality compared with conventional treatments.

ALLOGENEIC HCT

Even though myeloablative allogeneic HCT may be the only curative treatment in MM (due to its graft-versus-myeloma effect), its use has been limited to younger patients. Even with the limited indications, the toxic death rate related to infections and GVHD is considered too high and this strategy has been almost completely abandoned.[54]

Mortality can be reduced through the use of RIC regimens, and can be considered for older patients up to 65 years of age. However, when RIC-allogeneic transplant is used in patients with a high tumor burden or with chemotherapy-resistant disease, the immunologic effect of the graft is not sufficient to avoid relapses.[54] Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HCT.[54]

Section Summary: Allogeneic Hematopoietic Cell Transplantation

Studies have reported on patients with both myeloablative conditioning and RIC. Limitations of the published evidence include patient sample heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes, and inconsistency in reporting or collecting outcomes. Nonmyeloablative allo-HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allo-HCT improves survival better than autologous HCT.

POEMS SYNDROME

Systematic Reviews

In 2022, Kansagra published a retrospective analysis of 331 patients with POEMS syndrome from 92 centers between the years 2008-2018.[55] This study aims at providing help with decision-making tools in peri autologous HCT for patients and physicians of this rare disease. Here they assessed the non-relapse mortality (NRM), progression-free survival (PFS) and overall survival (OS) after HCT. The authors also compared the POEMS and MM and did not find any short or long-term NRM but patients with POEMS syndrome had a better PFS / OS compared ti MM at 5 years after autologous HCT. Of 331 patients, 16 (5%) patients developed SPM, including 4 (1.2%) myeloid malignancies and 12 (3.6%) new solid tumors, comparable to

MM with hematologic SPM of 2.8% and solid tumor SPM of 4.2% in patients not receiving maintenance lenalidomide after autologous HCT.

In 2012, Kuwabara performed a Cochrane review of HCT treatment of POEMS syndrome which identified no randomized controlled trials (RCTs), no quasi- RCTs, no historically controlled trials or trials with concurrent controls that met their study selection criteria.[56] The authors included six small series of patients (total n=57) who underwent autologous HCT. Two-year survival rates ranged from 94 to 100%. The review authors indicated that if all published experience with autologous HCT was pooled, transplant-related mortality would be three of 112 (2.7%). They caution that long-term outcomes with autologous HCT have not been elucidated and require continuing study.

A second 2012 review article indicated case series suggest most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m2.[5] Responses have been reported as durable but relapse occurs. Symptomatic progression has typically been reported as rare, with most progressions identified as rising vascular endothelial growth factor (VEGF) and radiographic. This author also reports that long-term outcomes with autologous HCT are unclear given the sparse numbers. However, a single-center series published in 2012 from Mayo Clinic reported a five-year OS of 94% and a PFS of 75% among 59 patients entered between 1999 and late 2011.[57] It is unlikely that randomized controlled trials of HCT in patients with POEMS syndrome will be feasible, given the rarity of the condition. The current evidence regarding HCT in patients with POEMS Syndrome consists mainly of small case series[58-66] (n<60) and review articles.[67-70] In addition, the criteria for diagnosing and treating the multiple potential symptoms associated with POEMS, has not been well defined. However, for autologous HCT, a chain of indirect evidence suggests improved health outcomes, as several case studies have reported good clinical responses in patients diagnosed with POEMS syndrome. Without larger treatment studies, the efficacy of allogenic and tandem HCT for patients with POEMS is unknown.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (MM) (v1.2024), including POEMS syndrome, provide the following[71]:

Autologous Transplant

For active (symptomatic) myeloma:

- If response to induction therapy:
  - Category 1 evidence supports proceeding directly to high-dose therapy and hematopoietic cell transplant. Delayed HCT can be considered in select patients, or
  - Continuous myeloma therapy or maintenance therapy, or Tandem Autologous Transplant (see below)
- If disease progression or relapse, additional treatment options include autologous HCT

Tandem Transplant

- NCCN recommends assessing for transplant candidacy at time of primary treatment and collecting enough stem cells for two transplants if appropriate.
- If response to primary (induction) therapy, tandem autologous HCT for patients with high-risk of progression/relapse under certain circumstances.

Allogeneic Transplant, including both myeloablative and reduced intensity

- If response to primary (induction) therapy, allogeneic HCT for patients with high-risk of progression/relapse under certain circumstances, and in the context of a trial when possible.
- If disease progression or relapse, additional treatment options include allogeneic HCT, in the context of a trial when possible.

POEMS Syndrome

The NCCN guidelines recommend autologous HCT in patients with POEMS syndrome who are eligible as sole therapy or as consolidation therapy after induction therapy.

(Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY (ASTCT)

The American Society for Transplantation and Cellular Therapy (ASTCT) (formerly the American Society for Blood and Marrow Transplantation, ASBMT), published updated clinical practice guidelines for transplantation and cellular therapies in Multiple Myeloma in 2022.[72]

ASTCT recommendations for patients with a new diagnosis of multiple myeloma:

Consensus Statements	Grade	Percentage of Panelists in Agreement
The panel recommends early autologous transplantation as a consolidation therapy in eligible, newly diagnosed myeloma patients after 4-6 cycles of induction	A	94.2%
The panel recommends mobilization and storage of peripheral blood stem cells in newly diagnosed patients not undergoing autologous transplantation after first line therapy for future use as treatment at first relapse.	B	100%
The panel does not recommend using MRD testing to guide use of autologous transplantation after induction therapy in myeloma, outside the setting of a clinical trial.	C	94.2%
The panel does not recommend age as the only selection factor when considering autologous transplantation in myeloma.	B	100%
In the absence of a clinical trial, the panel recommends early autologous transplantation in myeloma patients with high-risk cytogenetics [t (4;14); t (14;16); t (14;20)], 1p deletion, 1q gain/amplification and 17p deletion.	B	97.1%

Consensus Statements	Grade	Percentage of Panelists in Agreement
The panel does not recommend tandem autologous transplantation in standard risk myeloma patients after induction, outside in the setting of a clinical trial.	B	94.2%
The panel does not recommend routine multiagent consolidation therapy in patients with very good partial response or better after autologous transplantation outside the setting of a clinical trial.	B	85.7%
The panel does not recommend consolidation with CAR-T cell therapy in patients after first line therapy outside the setting of a clinical trial.	C	100%
The panel recommends lenalidomide maintenance after autologous transplantation in standard risk patients unless contraindicated.	A	94.2%
The panel recommends bortezomib and lenalidomide maintenance or clinical trial after autologous transplantation in high-risk patients.	B	82.8%
The panel does not recommend allogeneic transplantation except in the context of clinical trial.	C	91.4%
The panel does not recommend tandem autologous-allogeneic transplantation except in the context of clinical trial	C	88.5%
The panel recommends dose-adjusted melphalan in patients with renal impairment including on dialysis, >70 years and KPS<80.	B	82.8%
The panel recommends treating primary plasma cell leukemia similar to high-risk myeloma in the absence of a clinical trial.	B	97.1%

ASTCT recommendations for relapsed and refractory multiple myeloma:

Consensus Statement	Grade	Percentage of Panelists in Agreement
The panel recommends autologous transplantation in first relapse in patients who have not received transplant as first-line therapy.	A	94.2%
The panel recommends consideration of autologous transplantation in patients with primary refractory disease	C	85.7%
The panel recommends salvage second autologous transplantation in patients who were in remission for (at least) 36 months with maintenance and 18 months in the absence of maintenance	B	85.7%
The panel recommends CAR-T cell therapy after 4 or more prior lines of therapy	A	85.7%
The panel recommends clinical trial, If possible after CAR failures	B	97.1%
The panel encourages allogeneic transplantation in relapsed and/or refractory setting only in the context of clinical trial.	B	77.1%

Agency of Healthcare Research and Quality grading of recommendations based on level of evidence: A = There is good research-based evidence to support the recommendation; B = There is fair research-based evidence to support the recommendation; C = The

recommendation is based on expert opinion and panel consensus; X = There is evidence of harm from this intervention.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

In 2019, the American Society of Clinical Oncology (ASCO) published a practice guideline for the treatment of multiple myeloma (MM).[73] The guideline recommends offering up-front transplant to all eligible patients, although delayed HCT may be considered in select patients. Salvage or delayed HCT may be used as consolidation at first relapse in patients who choose not to proceed with HCT initially. Tandem autologous HCT and allogeneic HCT (allo-HCT) should not be routinely recommended. However, up-front tandem autologous HCT can be considered for select high-risk patients or those with a suboptimal response to the initial transplant; allo-HCT may be considered in select high-risk patients in the context of a clinical trial. For relapsed MM, autologous HCT, if not received after primary induction therapy, should be offered to transplant-eligible patients. Repeat HCT may be considered in relapsed MM if progression-free survival after the first transplant was 18 months or greater.

INTERNATIONAL MYELOMA WORKING GROUP RECOMMENDATIONS FOR TREATMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Recommendations for treatment of relapsed or refractory multiple myeloma were published in 2021.[74] For first relapse in patients with lenalidomide-refractory disease the recommendations state, “Consider salvage auto-transplantation in eligible patients.”

SUMMARY

MULTIPLE MYELOMA

There is enough research to show single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants for those with multiple myeloma may improve overall health outcomes. Outcomes include, but are not limited to, partial or complete response rates and prolongation of progression-free and overall survival. Practice guidelines based on research have specific recommendations for these regimes in specific patient populations. Therefore, single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants may be considered medically necessary in select patients when policy criteria are met.

There is not enough research to know if allogeneic hematopoietic cell transplant (including allo-HCT with myeloablative conditioning) improves overall health outcomes for those with multiple myeloma. Additionally, there is not enough research to know if single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants improves overall health outcomes when policy criteria are not met. Therefore, these treatment regimens are considered investigational unless policy criteria are met.

POEMS SYNDROME

There is enough research to show that overall survival may be improved with autologous hematopoietic cell transplant for those with POEMS syndrome. Therefore, this treatment may be considered medically necessary. Due to a lack of evidence, and practice guidelines,

allogeneic and tandem hematopoietic cell transplant are considered investigational to treat POEMS syndrome when policy criteria are not met.

REFERENCES

1. National Cancer Institute Physician Database Query (NCI PDQ®). Plasma Cell Neoplasms (Including Multiple Myeloma) Treatment (PDQ®)–Health Professional Version. June 30, 2023 [cited 10/02/2023]. 'Available from:' http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/HealthProfessional/#Section_4.
2. Palumbo A, Rajkumar SV. Treatment of newly diagnosed myeloma. *Leukemia.* 2009;23(3):449-56. PMID: 19005483
3. Kyle RA, Rajkumar SV. Multiple myeloma. *Blood.* 2008;111(6):2962-72. PMID: 18332230
4. Dispenzieri A. Long-term outcomes after autologous stem cell transplantation in patients with POEMS syndrome. *Clinical advances in hematology & oncology : H&O.* 2012;10(11):744-6. PMID: 23271262
5. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. *American journal of hematology.* 2012;87(8):804-14. PMID: 22806697
6. Bardwick PA, Zvaifler NJ, Gill GN, et al. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. *Medicine.* 1980;59(4):311-22. PMID: 6248720
7. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood.* 2003;101(7):2496-506. PMID: 12456500
8. Dispenzieri A. POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management. *American journal of hematology.* 2019;94(7):812-27. PMID: 31012139
9. Nasu S, Misawa S, Sekiguchi Y, et al. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. *Journal of neurology, neurosurgery, and psychiatry.* 2012;83(5):476-9. PMID: 22338030
10. Dispenzieri A. How I treat POEMS syndrome. *Blood.* 2012;119(24):5650-8. PMID: 22547581
11. Rajkumar SV, Kumar S. Multiple myeloma current treatment algorithms. *Blood Cancer J.* 2020;10(9):94. PMID: 32989217
12. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *American journal of hematology.* 2020;95(5):548-67. PMID: 32212178
13. Lin CM, Chang LC, Shau WY, et al. Treatment benefit of upfront autologous stem cell transplantation for newly diagnosed multiple myeloma: a systematic review and meta-analysis. *BMC Cancer.* 2023;23(1):446. PMID: 37193978
14. Gao F, Lin MS, You JS, et al. Long-term outcomes of busulfan plus melphalan-based versus melphalan 200 mg/m(2) conditioning regimens for autologous hematopoietic stem cell transplantation in patients with multiple myeloma: a systematic review and meta-analysis. *Cancer Cell Int.* 2021;21(1):601. PMID: 34758834
15. Mian H, Mian OS, Rochwerg B, et al. Autologous stem cell transplant in older patients (age>/=65) with newly diagnosed multiple myeloma: A systematic review and meta-analysis. *J Geriatr Oncol.* 2020;11(1):93-99. PMID: 31153809
16. Koreth J, Cutler CS, Djulbegovic B, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A

systematic review and meta-analysis of randomized controlled trials. *Biol Blood Marrow Transplant.* 2007;13(2):183-96. PMID: 17241924
17. Yong K, Wilson W, de Tute RM, et al. Upfront autologous haematopoietic stem-cell transplantation versus carfilzomib-cyclophosphamide-dexamethasone consolidation with carfilzomib maintenance in patients with newly diagnosed multiple myeloma in England and Wales (CARDAMON): a randomised, phase 2, non-inferiority trial. *The Lancet Haematology.* 2023;10(2):e93-e106. PMID: 36529145
18. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *N Engl J Med.* 2022;387(2):132-47. PMID: 35660812
19. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *The Lancet Haematology.* 2020;7(6):e456-e68. PMID: 32359506
20. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *New England Journal of Medicine.* 2017;376(14):1311-20. PMID: 28379796
21. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. *The lancet oncology.* 2015;16(16):1617-29. PMID: 26596670
22. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med.* 1996;335(2):91-7. PMID: 8649495
23. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med.* 2003;348(19):1875-83. PMID: 12736280
24. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood.* 1998;92(9):3131-6. PMID: 9787148
25. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood.* 2004;104(10):3052-7. PMID: 15265788
26. Blade J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood.* 2005;106(12):3755-9. PMID: 16105975
27. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol.* 2006;24(6):929-36. PMID: 16432076
28. Attal M, Harousseau JL. The role of high-dose therapy with autologous stem cell support in the era of novel agents. *Semin Hematol.* 2009;46(2):127-32. PMID: 19389496
29. Bensinger WI. Role of autologous and allogeneic stem cell transplantation in myeloma. *Leukemia.* 2009;23(3):442-8. PMID: 19277049
30. Villalba A, Gonzalez-Rodriguez AP, Arzuaga-Mendez J, et al. Single versus tandem autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma

and high-risk cytogenetics. A retrospective, open-label study of the PETHEMA/Spanish Myeloma Group (GEM). *Leukemia & lymphoma.* 2022;63(14):3438-47. PMID: 36124538
31. Lemieux C, Muffly LS, Rezvani A, et al. Outcomes with autologous stem cell transplant vs. non-transplant therapy in patients 70 years and older with multiple myeloma. *Bone Marrow Transplant.* 2021;56(2):368-75. PMID: 32782351
32. Marini C, Maia T, Bergantim R, et al. Real-life data on safety and efficacy of autologous stem cell transplantation in elderly patients with multiple myeloma. Ann Hematol. Germany, 2019:369-79.
33. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. *Biol Blood Marrow Transplant.* 2003;9(1):4-37. PMID: 12533739
34. Goldschmidt H, Baertsch MA, Schlenzka J, et al. Salvage autologous transplant and lenalidomide maintenance vs. lenalidomide/dexamethasone for relapsed multiple myeloma: the randomized GMMG phase III trial ReLApsE. *Leukemia.* 2021;35(4):1134-44. PMID: 32694619
35. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. *The lancet oncology.* 2014;15(8):874-85. PMID: 24948586
36. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *The Lancet Haematology.* 2016;3(7):e340-51. PMID: 27374467
37. Olin RL, Vogl DT, Porter DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. *Bone Marrow Transplant.* 2009;43(5):417-22. PMID: 18850013
38. Ikeda T, Mori K, Kawamura K, et al. Comparison between autologous and allogeneic stem cell transplantation as salvage therapy for multiple myeloma relapsing/progressing after autologous stem cell transplantation. *Hematological oncology.* 2019;37(5):586-94. PMID: 31674032
39. Qazilbash MH, Saliba R, De Lima M, et al. Second autologous or allogeneic transplantation after the failure of first autograft in patients with multiple myeloma. *Cancer.* 2006;106(5):1084-9. PMID: 16456814
40. Auner HW, Szydlo R, van Biezen A, et al. Reduced intensity-conditioned allogeneic stem cell transplantation for multiple myeloma relapsing or progressing after autologous transplantation: a study by the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2013;48:1395-400. PMID: 23708704
41. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial. *J Clin Oncol.* 2019;37(7):589-97. PMID: 30653422
42. Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 Protocol (BMT CTN 07LT). 05/11/2020 [cited 10/02/2023]. 'Available from:' https://clinicaltrials.gov/ct2/show/NCT02322320.
43. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol.* 2007;25(17):2434-41. PMID: 17485707

44. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2003;349(26):2495-502. PMID: 14695409
45. Stadtmauer EA. Multiple myeloma, 2004--one or two transplants? *N Engl J Med.* 2003;349(26):2551-3. PMID: 14695416
46. Maffini E, Storer BE, Sandmaier BM, et al. Long-term follow up of tandem autologous-allogeneic hematopoietic cell transplantation for multiple myeloma. *Haematologica.* 2019;104(2):380-91. PMID: 30262560
47. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *The lancet oncology.* 2011;12(13):1195-203. PMID: 21962393
48. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood.* 2008;112(9):3591-3. PMID: 18612103
49. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med.* 2007;356(11):1110-20. PMID: 17360989
50. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood.* 2006;107(9):3474-80. PMID: 16397129
51. Moreau P, Garban F, Attal M, et al. Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous transplantation in high-risk de novo multiple myeloma. *Blood.* 2008;112(9):3914-5. PMID: 18948589
52. Bjorkstrand B, Iacobelli S, Hegenbart U. Autologous stem cell transplantation (ASCT) versus ASCT followed by reduced-intensity conditioning allogeneic SCT with identical sibling donor in previously untreated multiple myeloma: preliminary analysis of a prospective controlled trial by the EBMT. *Bone Marrow Transplant.* 2008;41:S38. PMID:
53. Gahrton G, Iacobelli S, Bjorkstrand B, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. *Blood.* 2013;121:5055-63. PMID: 23482933
54. Harousseau JL. The allogeneic dilemma. *Bone Marrow Transplant.* 2007;40(12):1123-8. PMID: 17680016
55. Kansagra A, Dispenzieri A, Fraser R, et al. Outcomes after autologous hematopoietic cell transplantation in POEMS syndrome and comparison with multiple myeloma. *Blood Adv.* 2022;6(13):3991-95. PMID: 35507742
56. Kuwabara S, Dispenzieri A, Arimura K, et al. Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome. *The Cochrane database of systematic reviews.* 2012;6:CD006828. PMID: 22696361
57. D'Souza A, Lacy M, Gertz M, et al. Long-term outcomes after autologous stem cell transplantation for patients with POEMS syndrome (osteosclerotic myeloma): a single-center experience. *Blood.* 2012;120(1):56-62. PMID: 22611150
58. Barete S, Mouawad R, Choquet S, et al. Skin manifestations and vascular endothelial growth factor levels in POEMS syndrome: impact of autologous hematopoietic stem cell transplantation. *Archives of dermatology.* 2010;146(6):615-23. PMID: 20566924
59. Akkok CA, Holte MR, Tangen JM, et al. Hematopoietic engraftment of dimethyl sulfoxide-depleted autologous peripheral blood progenitor cells. *Transfusion.* 2009;49(2):354-61. PMID: 18980622

60. Dispenzieri A, Moreno-Aspitia A, Suarez GA, et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. *Blood.* 2004;104(10):3400-7. PMID: 15280195
61. Jaccard A, Royer B, Bordessoule D, et al. High-dose therapy and autologous blood stem cell transplantation in POEMS syndrome. *Blood.* 2002;99(8):3057-9. PMID: 11929800
62. Dispenzieri A, Lacy MQ, Hayman SR, et al. Peripheral blood stem cell transplant for POEMS syndrome is associated with high rates of engraftment syndrome. *European journal of haematology.* 2008;80(5):397-406. PMID: 18221391
63. Gupta S, Rana V, Chandra D, et al. Autologous peripheral stem cell transplant for POEMS syndrome: a case report. *Hematology.* 2006;11(5):361-3. PMID: 17607587
64. Jang IY, Yoon DH, Kim S, et al. Advanced POEMS syndrome treated with high-dose melphalan followed by autologous blood stem cell transplantation: a single-center experience. *Blood research.* 2014;49(1):42-8. PMID: 24724066
65. Ishii Y, Yamazaki E, Ishiyama Y, et al. Successful treatment of POEMS syndrome with bortezomib and dexamethasone, combined with radiotherapy, and followed by autologous stem cell transplantation. *International journal of hematology.* 2013;98(6):723-8. PMID: 24166587
66. Keyzner A, D'Souza A, Lacy M, et al. Low levels of interleukin-1 receptor antagonist (IL-1RA) predict engraftment syndrome after autologous stem cell transplantation in POEMS syndrome and other plasma cell neoplasms. *Biol Blood Marrow Transplant.* 2013;19(9):1395-8. PMID: 23792270
67. Mendez-Herrera CR, Cordovi-Rodriguez D. [POEMS syndrome: a review of the literature]. *Revista de neurologia.* 2011;53(1):44-50. PMID: 21678324
68. Dispenzieri A. POEMS syndrome. *Blood reviews.* 2007;21(6):285-99. PMID: 17850941
69. Dispenzieri A, Gertz MA. Treatment options for POEMS syndrome. *Expert opinion on pharmacotherapy.* 2005;6(6):945-53. PMID: 15952922
70. Dispenzieri A, Gertz MA. Treatment of POEMS syndrome. *Current treatment options in oncology.* 2004;5(3):249-57. PMID: 15115653
71. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Multiple Myeloma. v.1.2024. [cited 10/02/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.
72. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Multiple Myeloma. 03/16/2022 [cited 10/06/2023]. 'Available from:' http://tgapp.asbmt.org/#/article-summary-tctmm-page.
73. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. *J Clin Oncol.* 2019;37(14):1228-63. PMID: 30932732
74. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *The lancet oncology.* 2021;22(3):e105-e18. PMID: 33662288

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous

	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

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